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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/991,073
Filing Date: November 14, 2001
Appellant(s): BOTSTEIN ET AL.

Daphne Reddy
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/22/2005 appealing from the Office action mailed 2/23/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

In addition to the antibody and nucleic acid cases disclosed by Appellants, the Examiner notes that there are a multitude of applications that are also in prosecution or under appeal that are drawn to different protein or nucleic acid sequence, but involve the same issues on appeal with regard to 35 U.S.C. §101 and §112, first paragraph (enablement); for example, see 09/904766 and 10/145124.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

A substantially correct copy of appealed claims 122-126 and 129-131 appears on pages 29-30 of the Appendix to the appellant's brief. The minor errors are as follows: Claims 122 and 123 commence with the word "An", not "The".

(8) Evidence Relied Upon

Sen, 2000, Curr. Opin. Oncol. 12:82-88.

Pennica et al., 1998, PNAS USA 95:14717-14722..

Hu et al., 2003, Journal of Proteome Research 2:405-412.

Hanna et al., 1999, Pathology Associates Medical Laboratories.

Ornfoft, Molecular & Cellular Proteomics 1:37-45, (2002).

Hyman, Cancer Research 62 6246-6245, Novemher (2002).

Pollack, PNAS Vol.99, 20:12963-12968, October (2002).

Hillier et al., Locus H74302, WashUMerck EST project (1995).

Sibson et al., WO94/01548, 1994.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 122-126 and 129-131 are rejected under §35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility.

The specification discloses a protein designated PRO809, and nucleic acid encoding such. There is no discussion of the structure of the protein encoded by the claimed nucleic acids, nor disclosure of any relationship between such structure and a purported function. There is no disclosure of any disease or condition in any way related to the nucleic acids that encode the claimed protein, nor disclosure of any diagnostic or analytical assay that could be performed using the claimed proteins.

The claims are directed to isolated polypeptides having at least 95% identity to a SEQ ID NO: 223 with or without its signal peptide. Finally, claims are presented to chimeric proteins comprising the aforementioned polypeptides. The specification contains numerous asserted utilities including use to identify molecules that bind to PRO809 (including agonists and antagonists), to make "knock-out" mice or other animals, in gene therapy, as molecular weight markers, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed PRO809 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO809.

Utility must be in readily available form. In Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct,.1966), a process of producing a novel compound that was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be useful because the compound produced thereby was potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The instant claims are drawn to a polynucleotide encoding a protein which has undetermined function or biological significance. Until some actual and specific activity can be attributed to the protein identified in the specification as PRO809 protein or the polynucleotides encoding it, the claimed invention is incomplete. Merely using the polynucleotides to determine the properties of the encoded protein does not constitute a patentable utility.

It is further noted that the nucleic acid encoding the claimed PRO809 polypeptide is disclosed as having given positive results in a single assay, Example 170 beginning at page 539 of the specification, a gene amplification assay. Therein, PRO809 was found to be amplified approximately two fold in 3 of 10 human lung tumor squamous cell carcinoma cell lines, 2 of 9 human lung tumor adenocarcinoma cell lines, and the sole human lung tumor large cell

carcinoma cell line. The finding that the genomic nucleic acid encoding PRO809 is amplified, likely indicating aneuploidy, in the aforementioned tumor types is insufficient to confer utility to the nucleic acid. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. In this case, the sequence of PRO809 was found at no more than two copies per cell, and only in a minority of tumors tested. The person of ordinary skill in the art would not consider the results to be significant or diagnostic in view of the review by Sen. Even *if* such were sufficient to confer utility to the nucleic acids, such would not be indicative of a use of the encoded polypeptide as a diagnostic or therapeutic agent. As stated above, slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Also, the literature reports that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the claimed polypeptides would be useful for diagnosis of cancer or as a drug target. For example, Pennica et al. (1998, PNAS USA 95:14717-14722) disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." Therefore, data pertaining to PRO809 nucleic acids do not necessarily indicate anything significant regarding the claimed PRO809 polypeptides. Thus, the data do not support the implicit assertion that PRO809 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to

determine whether PRO809 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 122-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 122-124 and 130-131 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

It is noted that applicants have amended the claims during prosecution to recite that the nucleic acid encoding the claimed polypeptide is "amplified in lung tumors". There is no written description for the breadth of proteins that are 95 or 99% identical to SEQ ID NO: 223 and are amplified in lung tumors, because (a) no significant association between the disclosed nucleic acids and lung cancer, such as would lend diagnostic utility, has been disclosed or established,

and (b) even if such *had* been established, it would not be predictable that the claimed protein would be similarly diagnostic for reasons cited in the rejection under 35 U.S.C. §101, above. All the specification discloses is a single nucleic acid and a single putative protein thought to be encoded by that nucleic acid; such does not provide a description of variants that *might* be found in lung tumors; not a single sequence has been isolated *from* a lung tumor.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity, and a hypothesis that the sequence might become altered in lung tumors. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine

sequence. In this case, all that is provided is a nucleic acid that is asserted (unconvincingly, in the Examiner's opinion) to be associated with lung tumors, and an inkling of an idea that the protein encoded by the nucleic acid might be found to be altered in sequence in lung tumors, based solely upon the minor amplification of the genomic DNA that encodes the protein in tested cell lines.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 223, with or without the signal sequence, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 122-126 and 129-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over clone H74302, isolated by L. Hillier et al., WashUMerck EST Project 1995 in view of Sibson et al., WO94/01548.

By applicants admission at page 454 of the specification, the clone that was sequenced and designated DNA57836-1338 or PRO809, was purchased from Merck under clone designation H74302. According to NCBI, the cDNA was double stranded, and inserted in the "Lafmid BA vector", which was propagated in E. coli cells. With respect to claim 136, the DNA

would necessarily have been "operably linked" to sequences in the vector for control of replication of the vector.

Sibson et al. disclose that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Fusion proteins are disclosed at page 8 as being useful for affinity purification of the desired protein. The person of ordinary skill in the art would recognize the moiety used in the fusion protein for such purpose as being an epitope tag.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA disclosed by applicants admission of H74302 to express and then isolate the encoded polypeptide either alone or as a fusion protein as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above.

(10) Response to Argument

At page 4 of the Brief, appellants assert that an amplification of 2-3 fold in different lung primary tumors is significant, and refer to a declaration by Dr. Goddard in support of the assertion. This argument has been fully considered but is not deemed persuasive. The Examiner notes that the 2-3 fold amplification was found in a small minority of the cell lines tested: genomic PRO809 DNA was found to be amplified approximately two-fold in 3 of 10 human lung tumor squamous cell carcinoma cell lines, 2 of 9 human lung tumor adenocarcinoma cell lines, and the sole human lung tumor large cell carcinoma cell line. No causality has been established, i.e. there is no link between the increased genomic DNA and the development of any cancer, and no protein data are presented; appellants have not examined whether the protein encoded by the PRO809 DNA is expressed *at all, in any type of tissue*, much less in cancer. As stated in the rejection above, and evidenced by the Sen reference, the most parsimonious explanation for the observed result is aneuploidy. Further, the slight amplification of genomic DNA (2-3 fold), either via aneuploidy or partial duplication of the gene, would not predictably lead to amplification of the protein product. The declaration under 37 C.F.R. §1.132 by Dr.

Goddard has been fully considered. The Goddard declaration is not pertinent, as it is drawn to the significance of the amplification of the nucleic acids, and fails to address the issue of the claimed antibodies, which bind to the protein encoded by the nucleic acid which is alleged to be significantly amplified in cancer.

If the claims were directed to nucleic acids, the Goddard declaration would be found as follows:

Declarant discusses the accuracy of the Taq DNA polymerase assay, stating that the Taqman PCR technique is sensitive enough to detect at least a 2-fold increase in gene copy number (paragraph 3) and that this increase is significant and useful. This argument has been fully considered but is not deemed persuasive because it evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO809 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO809 nucleic acid was amplified in some cancers, to a minor degree (about 2.5-5 fold). No mutation or translocation of PRO809 has been associated with any type of cancer versus normal tissue. It is not known whether PRO809 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO809 is amplified in a variety of samples, including some normal tissues, and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is due to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. It remains that, as evidenced by Pennica et al., the issue is simply not predictable, and the specification presents a mere invitation to experiment.

Furthermore, the Declaration does not provide data such that the examiner can independently draw conclusions. Only Doctor Goddard's conclusions are provided in the declaration. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there

was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Therefore, the Goddard declaration is not persuasive as it relates only to the issue of nucleic acid and not to the claimed subject matter, which is antibodies, and further, *if* the claims were directed to nucleic acids, would still have not been persuasive.

At page 5, appellants argue that "the art exemplified by the Hittelman *et al.* reference and Sen *et al.*, as well, still supports the Appellants position that, whether aneuploidy is a feature of cancerous, pre-cancerous or damaged tissue, it still provides utility for the PRO809 gene as a marker. This argument has been fully considered but is not deemed persuasive. First, the Examiner notes there is no "Hittleman" reference of record in this case; accordingly, such will not be addressed. However, it remains that the PRO809 genomic amplification was minimal, and that the most parsimonious explanation is aneuploidy, with no evidence that the chromosome bearing PRO809 was preferentially amplified (as opposed to other chromosomes). Aneuploidy is also a feature of damaged tissue, and is commonly found in lung tissues, which are subject to constant environmental damage. It does not invariably or inevitably lead to cancer; rather, such damaged cells are generally removed by the body; the development of cancer is the exception, as evidenced by the fact that the general population is constantly suffering damage to lung cells via air pollution, whereas lung cancer remains relatively rare. Further, it remains that the 2-3 fold amplification of the nucleic acid is consistent with a simple case of aneuploidy, in which there is a single extra copy of the chromosome in question, and is *not* predictive of a similar differential in protein expression; hence, the argument is not persuasive, as the claims are drawn to polypeptides, not the nucleic acids that encode them. Merely because amplification *may* be an *initial* step in the formation of cancer does not equate with a substantial assertion of diagnostic utility for the encoded protein.

At page 5, Appellant argues that Orntoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification increased mRNA expression. Appellant points to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on Nov. 4 2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellant asserts that the

research community believes that the information obtained from gene chips is useful. Finally, Appellant concludes that, while there may be exceptions, there is generally a good correlation between gene amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO809 conveys utility to the claimed PRO809 polypeptides. This has been fully considered but is not found to be persuasive. While Pennica et al. is directed to small numbers of genes, the instant application concerns only one gene as well. Furthermore, Hu et al., speaks to larger sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

Also at page 5, Appellant presents a discussion of the declaration by Dr. Polakis filed under 37 CFR 1.132 with the response. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO809 in tumor samples relevant to normal samples. Only gene amplification data was presented. Therefore, the declaration is insufficient to overcome the rejection of claims based upon 35 U.S.C. §101 and §112, first paragraph, since it is limited to a discussion of data

regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). . By appellants admission, the amplification of the PRO809 genomic DNA is in the 2-3 fold range, well below five-fold.

Thus, appellants conclusion that for the "majority" of amplified genes gene amplification influences gene expression at the mRNA and protein levels is misleading. What the art teaches is that there is such a correlation for *highly* amplified genes, which PRO809 is not. The art does *not* teach such predictability for the amounts of amplification observed for PRO809. Hu, in particular, leads to the conclusion that for the amount of amplification found by appellants for PRO809, such a correlation is *not* expected. The art further teaches that such correlations are not accepted on the basis of gene amplification data alone, but rather that the standard in the art, as evidenced by Hu, is to actually *do* the experiments, that is, to *look* at protein levels, something appellants have not done.

At p. 6 of the Brief, Appellant argues that, even if there were no correlation between gene amplification and increased mRNA/polypeptide expression, a polypeptide encoded by a gene that is amplified in cancer would still have utility in that simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification,

leading to a better determination of a suitable therapy, as demonstrated by the real-world example of the breast cancer marker HER-2/neu. Hanna et al. teaches that the HER-2/neu gene is over-expressed in breast cancers, and teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene as well as over- expression of the HER-2/neu gene product. Appellant argues that the disclosed assay (of Hanna) leads to a more accurate classification of the cancer and a more effective treatment of it. The examiner agrees. In fact, Hanna et al. supports the instant rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Appellant points to the Ashkenazi declaration as supporting the above point. This has been fully considered but is not found to be persuasive, since the specification does not disclose that the PRO809 polypeptide levels increase **or** stay the same, or even that the protein is expressed at all. Further research would be needed to reasonably confirm whether or not there is a change in PRO809 polypeptide levels in cancers showing gene amplification of PRO809 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO809 polypeptide as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides.

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene *products* (such as the claimed polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial.

At page 7, appellant argues that the claimed genus has been described sufficiently by the recitation of both structural and functional characteristics. This argument has been fully

considered but is not deemed persuasive. It is noted that the recitation "the nucleic acid encoding said polypeptide is amplified in lung tumors" is not a functional recitation *per se,* but rather a descriptor of where one might encounter the nucleic acids. Appellants have not established that there is any conception of nucleic acids in a manner commensurate in scope with the claims, and hence of the claimed polypeptides. All applicants have presented is a single nucleic acid found to be slightly amplified in a small proportion of cancer cell lines, and the germ of an idea that there might be variants of the nucleic acid that would be similarly associated. There is no evidence of the actual conception of such nucleic acids, nor is there any evidence of record that they exist. Hence, there is accordingly no written description of the claimed polypeptides, other than the one identified as SEQ ID NO: 223. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

At pp. 8-11 of the Brief, Appellant reviews the legal standard for utility, with which the examiner takes no issue.

At page 12 of the Brief, Appellant argues that the data in Example 170 describes results of a gene amplification assay. Appellant characterizes the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellant asserts that gene amplification is an essential mechanism for oncogene activation. Appellant reviews how the assay was performed, and reports that the gene encoding PRO809 was significantly amplified (2-3-fold) in five lung primary tumors. Appellant argues that it is well known that gene amplification occurs in most solid tumors, and is generally associated with poor prognosis. Appellant refers to the declaration of Dr. Goddard. Appellant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the amplification of the gene encoding PRO809 in 5 tumors is credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. This line of argument and the Goddard declaration are relevant to the utility of the PRO809 **DNA**, but not the PRO853 **polypeptide**. As discussed above, the art shows that

increased DNA levels are not predictive of increased mRNA levels, and that increased mRNA levels are not predictive of increased polypeptide levels.

At page 13, appellants argue that PRO809 would have utility even if it were associated with a malignancy of rare occurrence. This argument has been fully considered but is not deemed persuasive because there is no association established on the record that PRO809 is associated with any malignancy, much less a rare one. Example 170 is one in which levels of PRO809 *genomic DNA* were measured in a number of tumor cell lines, and found to be minimally amplified by 2-3 fold in a minority of lung cancer cell lines tested. As stated repeatedly above, there is (a) no causality shown between the amplification of PRO809 genomic DNA and any cancer or tumor, as the most parsimonious explanation is aneuploidy, which is often non-specific phenomenon, (b) there are *no* data of record pertaining to the claimed protein. Applicants argument at page 13 is an example of wishful thinking, that is, that if one were to perform substantial further experimentation (of the type that the Examiner considers to be part of the act of invention itself), that one *might* someday find such a correlation. No rare cancers have been examined here, no protein has been assayed here. All we have is an invitation to experiment to determine *if* the claimed PRO809 polypeptides *might* someday prove to have utility.

At page 14, appellants reiterate their argument of the Ashkenazi declaration, which remains non-persuasive for reasons cited above. Ashkenazi does not discuss the claimed invention, which is protein.

Also at page 14, appellants argue that Sen supports their position that even aneuploidy can be useful to diagnose a propensity for cancer, and that "Many articles" published around the filing date studied damaged or premalignant lesions and suggested that epithelial tumors develop through a multistep process..." This argument has been fully considered but is not deemed persuasive because the claims under appeal are directed to polypeptides. Even *if* aneuploidy is useful as a diagnostic, the issue here is that it is not predictive of protein levels. It remains that it has not been shown what, if any, tissues PRO809 polypeptide is expressed in; not normal, not precancerous, not cancerous. It also remains that the art, as cited by the Examiner, teaches that

amplification of genomic DNA in a manner consistent with that shown for PRO809 is *not predictive* of protein levels. It further remains that no causality or consistent correlation has been established between the observed 2-3 fold amplification of PRO809 *genomic DNA* and any cancer, much less between the claimed polypeptides and such. The cell lines that were tested are alleged to have been from cancers. There are no data regarding risk assessment, no date pertaining to damaged tissue, and no data pertaining to precancerous tissue. Finally, the Examiner has cited specific prior art to support her assertions. Appellants, during the prosecution, provided additional references, which the Examiner has addressed and found to actually support the finding of lack of utility. The Examiner is unable to respond to the assertion at page 14 that there are "many articles" that support their position, in the absence of any specific citations.

It is noted that all the prior art under consideration appeared in peer-reviewed publications. Appellants repeatedly try to impugn the statistical methods used therein, by general allegation. The Examiner finds no merit in this argument.

At page 16, with respect to the Hu reference, appellants again urge that a paper to a particular type of breast tumor cannot be generalized as a principle governing microarray study of breast or other cancers in general. Appellants are urging an improper standard. The Examiner has cited relevant art. *If* art existed to demonstrate facts for PRO809 in particular, she would have cited that, but it does not exist. Therefore, one must turn to the art as a whole for guidance. Appellants repeatedly try to impugn references for being drawn to different genes than PRO809, or different types of cancers, but have provided no more "relevant", e.g. closer to the instant fact situation, data or references. Accordingly, the record must be judged for what the cited references teach. Hu's "class" of genes provides substantially more evidence than the instant specification. Appellants have pointed to no factual error in the Examiner's conclusion that Hu's paper indicates that genes that are amplified 5-fold or less show no evidence of a correlation between altered gene expression and a known role in disease. It is now notoriously well known in the art that a gene is transcribed to mRNA, with any where from one to many copies of mRNA being made from a single copy of a gene. Each mRNA is then translated to protein, with anywhere from one to many copies of protein being made per mRNA. Thus, logically, if Hu

concludes that a correlation between *mRNA and protein* cannot be made, it follows that a correlation between *DNA and protein*, as urged by appellants, is more greatly lacking in merit.

At pp. 16-20 of the Brief, Appellant argues that ample evidence has been submitted to support the assertion that gene amplification more likely than not correlates with increased mRNA and polypeptide levels. Appellant characterizes Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellant characterizes Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellant characterizes Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Appellant concludes that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Hyman does not examine protein expression. Hyman states that only 44% of *highly amplified genes*, which Hyman defines (Fig. 1A) as greater than 2.5 CGH (normalized to housekeeping genes) showed overexpression. None the values identified by appellants for PRO809 would be considered to be highly amplified as disclosed by Hyman. It is further noted that Hyman standardized to 88 housekeeping genes (p. 6241, left column); the instant specification includes no such standardization. Thus, comparing Hyman's

data to appellants, it can be concluded that (a) PRO809 was not assayed in a fashion that one could conclude it to be "highly amplified" as the term is used by Hyman, and (b) that even if it were, there would only be a 44% chance that the "highly amplified" state would be reflected in protein levels for lung cancers. As Hyman did not look at lung tumors, one can either conclude that they would be similar to what was found for breast cancer, in which case it is more likely than not that there would be no correlation between gene amplification and cancer, or that they would be dissimilar, in which case there is even *less* predictability. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

At pp. 17 and 20-21 of the Brief, Appellant refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132. Appellant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellant concludes that all of the submitted evidence supports Appellant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO809 (i.e., data regarding amplification of PRO809 genomic DNA), and does not disclose

any information regarding PRO809 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al. and Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

The Ashkenazi declaration was considered above, to whit: "The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. The examiner agrees that evidence regarding lack of over-expression would be useful. However, there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Further research is required to determine such. Thus, the asserted utility is not substantial."

At p. 22 of the Brief, Appellant urges that Hanna et al. support Appellant's position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Specifically, Appellant argues that, while some subsets of tumors were found lacking protein overexpression with gene amplification, in general the results correlated well. This has been fully considered but is not found to be persuasive. Hanna et al. clearly show that the skilled artisan does not assume that any tumor with a HER-2/neu gene amplification event also overexpressed HER-2/neu protein. It is tested empirically. In stark contrast to PRO809, HER-2/neu was already known to be a tumor associated gene. Hanna did not draw that conclusion based upon the type of date presented in the instant specification. Finally, both FSH and IHC directly assay protein, and thus would be expected to correlate well with each other. The issue in

the instant case is not whether one protein assay is comparable to another, but whether a 2-3 fold amplification of genomic DNA would be considered to be reasonably predictive of overexpression of the encoded protein.

At page 23 of the Brief, Appellant argues that even if gene amplification does not result in overexpression of the encoded polypeptide, an analysis of the expression of the polypeptide is useful in determining the course of treatment, as suggested by the Ashkenazi declaration. Appellant argues that the examiner mischaracterizes the testing described in the Ashkenazi declaration as involving further characterization of the PRO809 polypeptide itself. Appellant urges that the purpose of the testing is not to further characterize the PRO809 polypeptide, but to further characterize the tumors being sampled. Appellant concludes that the PRO809 polypeptides and antibodies which specifically bind thereto are useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling selection of a treatment modality that holds the most promise for the successful treatment of a patient. This has been fully considered but is not found to be persuasive. First, testing whether or not a polypeptide is overexpressed in a particular tumor yields information regarding the tumor *and* the polypeptide itself. For example, a polypeptide can be further categorized regarding its expression pattern in healthy and diseased tissues. Second, the specification does not assert that PRO809 polypeptide is useful as a tumor categorization agent. Such is only presented in the arguments and declaration. Third, even if such were asserted in the specification as filed, the skilled artisan would still have to perform further research to reasonably confirm whether or not PRO809 polypeptide is overexpressed in any tumor, since the expression levels of PRO809 polypeptide are not disclosed in the specification. The requirement for such further research indicates that the utility is not in currently available form, i.e., it is not substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna et al., Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO809 polypeptide. Identifying a drug specific for PRO809 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO809 polypeptide and on tumor),

considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

In conclusion, it is noted that M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO809 polypeptides are useful as diagnostic markers for cancer or as therapeutic targets for cancer drugs is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO809 polypeptide to be useful as a cancer diagnostic or therapeutic target, there must be a detectable change in the amount or form of PRO809 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al.), and (2) increased mRNA levels do not reliably correlate with increased polypeptide levels (Hu et al., Hanna et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO809 polypeptides can be used as a cancer diagnostic agent.

At page 24-25, appellants discuss the standards for determining written description. No comment by the Examiner is necessary.

At page 25, appellant argues that SEQ ID NO: 223 has been reduced to practice, an issue not contested by the Examiner. Appellant further argues that the specification provides guidance as to how to alter the protein of SEQ ID NO: 223 and identify whether a variant of such falls within the metes and bounds of the claims. This argument has been fully considered but is not deemed persuasive because the claims are not drawn to engineered variants of the protein of SEQ ID NO: 223, but rather require that "the nucleic acid encoding said polypeptide is amplified in lung tumors." The only nucleic acid that has been shown to be amplified, (2-3 fold) in any lung tumor is that of SEQ ID NO: 222. There has been no conception of any other nucleic acid

being amplified in such tumors. The issue of engineering a protein in a manner that would retain protein function is moot (note that there is also no function known for PRO809).

At page 26, appellants argue that the recitation of a functional property in the claims overcomes the rejection. It is noted that the recitation "the nucleic acid encoding said polypeptide is amplified in lung tumors" is not a functional recitation *per se,* but rather a descriptor of where one might encounter the nucleic acids. This argument has been fully considered but is not deemed persuasive because applicants have not established that there is any conception of nucleic acids in a manner commensurate in scope with the claims, and hence of the claimed polypeptides. All applicants have presented is a single nucleic acid found to be slightly amplified in a small proportion of cancers, and the germ of an idea that there might be variants of the nucleic acid that would be similarly associated. There is no evidence of the actual conception of such nucleic acids, nor is there any evidence of record that they exist. Hence, there is accordingly no written description of the claimed polypeptides, other than the one identified as SEQ ID NO: 223. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. In this case, appellants have found a single nucleic acid that exists in slightly increased copy number in a minority of cancer cell lines, and invite one to imagine that there is causality between the DNA sequence and cancer, that the protein encoded by that DNA is expressed in a manner that would allow use as a diagnostic, and further, that the sequence of that protein would be altered in some such cancers, and seeks to claim such altered proteins. The Examiner maintains that such is merely wishful thinking, and that there is neither conception or written description of such variants.

Appellant argues the art rejection at pages 27-28 of the Brief. Appellant argues that the Hillier EST clone does not disclose or reduce to practice the protein of SEQ ID NO: 223, that Hillier does not disclose that their EST was part of a cDNA that coded for a protein, and that Hillier's sequence lacks the C-terminus of the cDNA. As stated in the grounds of rejection, by applicants admission at page 454 of the specification, the clone that was sequenced and

designated DNA57836-1338 or PRO809, was purchased from Merck under clone designation H74302. In fact, the specification at page 454 states "the Merck EST clone H74302 was purchased and the cDNA insert was obtained and sequence. It was found that this insert encoded a full-length protein. The sequence of this cDNA insert is shown in Figure 150 and is herein designated DNA57836-1338." The Examiner is at a loss as to how appellants can argue that the sequence that they disclose as having been obtained from a purchased clone can differ from itself. There is no disclosure in the specification of having obtained any additional sequence. Therefore, the Examiner is at a loss as to how there could possibly exist any differences between appellants clone and the one they purchased, as the purchased clone is the *sole* disclosure of how PRO809 was obtained. Any sequence outside the coding region is not relevant, as it is protein that is being claimed herein. The clone was clearly available from Merck and marketed as a cDNA clone. One of ordinary skill in the art knows that cDNA is generated from mRNA, and thus represents a molecule used by the source cell for making protein (note that this is a distinct situation from those discussed above, in which the Examiner has found that the presence of *genomic* DNA is not predictive of protein). Accordingly, one of ordinary skill in the art purchasing a cDNA clone from Merck would expect that clone to encode one or more proteins. Appellants have repeatedly failed to address this crucial issue, namely that the specification acknowledges that appellants did not isolate the cDNA themselves, but rather bought it from a commercial source. Appellants allege that they have provided an alignment of Hillier's sequence with theirs. However, the Examiner is at a loss as to how the two sequences can possibly be different, as the specification cites Hillier's clone as the source, and further, no alignment of the encoded *proteins* has been provided.

Appellants argument also constitutes a piecemeal analysis of the references cited in the rejection. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, appellants acknowledge in the specification that they bought a cDNA clone. Sibson teaches that it is generally useful to place a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such cDNA's. See pages 8-13. Fusion proteins are disclosed at page 8 as being useful for affinity

purification of the desired protein. The person of ordinary skill in the art would recognize the moiety used in the fusion protein for such purpose as being an epitope tag.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use the DNA disclosed by applicants admission of H74302 to express and then isolate the encoded polypeptide either alone or as a fusion protein as taught by Sibson et al. in view of Sibson et al.'s suggestion that it would be desirable to do so, as cited above. All that is needed to meet the standard of obviousness here is that the person of ordinary skill in the art would have been motivated to express the protein encoded by a commercially available clone. Sibson clearly teaches that one would be desirous of doing so with *any* cDNA clone.

Finally, although not explicitly argued, appellant may be trying to intimate that Hillier's clone does not meet the limitations of the claims because the encoded protein is shorter than that of appellants' SEQ ID NO: 223 (although as explained above, the Examiner cannot determine the source of the additional sequence). Even *if* there were a difference in length between the protein encoded by the bought clone and SEQ ID NO: 223, the protein encoded by the bought clone would meet the claimed limitations, as it is routine to calculate percentage identity relative to the shorter of two sequences being compared. Thus, a sequence of 215 amino acids that matched the relevant portion of SEQ ID NO: 223 with 100% identity would be considered to be 100% identical to SEQ ID NO: 223.

Applicants argument at page 16 of the response has been fully considered but is not deemed persuasive. The specification clearly states that the clone was purchased from Merck, and sequenced to obtain the sequence identified as PRO809. Applicants allegation to the contrary, in the absence of evidence, is not persuasive. In order to overcome this rejection, applicants must submit evidence in appropriate form as to what the actual sequence of the clone was, including an alignment to the claimed nucleic acids, in order for the Examiner to make a factual determination contrary to the admissions in the specification.

(11) Related Proceeding(s) Appendix

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Lorraine Spector
Primary Examiner

Conferees:

Brenda Brumback
Supervisory Primary Examiner

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Janet Andres
Supervisory Primary Examiner

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER